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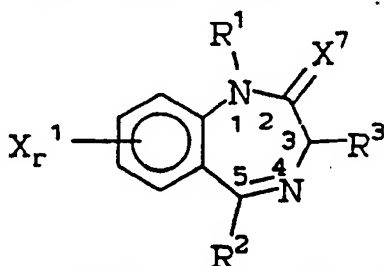
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54 New benzodiazepine analogs.

57 Benzodiazepine analogs of the formula :



I

are disclosed which are antagonists of gastrin and cholecystokinin (CCK) with enhanced aqueous solubility and have properties useful in the treatment of disorders of gastric secretion, appetite regulation, gastrointestinal motility, pancreatic secretion, and dopaminergic function, as well as in treatment producing potentiation of morphine and other opiate analgesics.

EP 0 434 369 A1

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NEW BENZODIAZEPINE ANALOGS

CROSS-REFERENCE

Starting materials for the compounds of Formula I are prepared and described in U.S. Patent 4,820,834
 5 and B. Evans et al., J. Med. Chem. 31, 2235-2246 (1988).

BACKGROUND OF THE INVENTION

Cholecystokinins (CCK) and gastrin are structurally-related neuropeptides which exist in gastrointestinal
 10 tissue and in the central nervous system (see, V. Mutt, Gastrointestinal Hormones, G. B. J. Glass, Ed., Raven Press, N.Y., p. 169 and G. Nisson, *ibid.*, p. 127).

Cholecystokinins include CCK-33, a neuropeptide of thirty-three amino acids in its originally isolated form
 (see, Mutt and Jorpes, Biochem. J. 125, 678 (1971)), its carboxyl terminal octapeptide CCK-8 (a naturally-occur-
 15 ring neuropeptide, also, and the minimum fully active sequence), and 39- and 12-amino acid forms, while gastrin
 occurs in 34-, 17- and 14-amino acid forms, with the minimum active sequence being the C-terminal tetrapeptide
 Trp-Met-Asp-Phe-NH₂, which is the common structural element shared by both CCK and gastrin.

CCK's are believed to be physiological satiety hormones, thereby possibly playing an important role in
 appetite regulation (G. P. Smith, Eating and Its Disorders, A. J. Stunkard and E. Stellar, Eds, Raven Press,
 New York, 1984, p. 67), as well as also stimulating colonic motility, gall bladder contraction, pancreatic enzyme
 20 secretion, and inhibiting gastric emptying. They reportedly co-exist with dopamine in certain mid-brain neurons
 and thus may also play a role in the functioning of dopaminergic systems in the brain, in addition to serving as
 neurotransmitters in their own right (see : A. J. Prange et al., "Peptides in the Central Nervous System", Ann.
Repts. Med. Chem. 17, 31, 33 [1982] and references cited therein ; J. A. Williams, Biomed. Res. 3 107 [1982];
 and J. E. Morley, Life Sci. 30, 479, [1982]).

The primary role of gastrin, on the other hand, appears to be stimulation of the secretion of water and elec-
 25 trolytes from the stomach, and, as such, it is involved in control of gastric acid and pepsin secretion. Other
 physiological effects of gastrin include increased mucosal blood flow and increased antral motility, with rat
 studies having shown that gastrin has a positive trophic effect on the gastric mucosa, as evidenced by increased
 DNA, RNA and protein synthesis.

Antagonists to CCK and to gastrin have been useful for preventing and treating CCK-related and/or gas-
 30 trin-related disorders of the gastrointestinal (GI) and central nervous (CNS) systems of animals, especially of
 humans. Just as there is some overlap in the biological activities of CCK and gastrin, antagonists also tend to
 have affinity for both receptors. In a practical sense, however, there is enough selectivity to the different recep-
 tors that greater activity against specific CCK- or gastrin-related disorders can often also be identified.

Selective CCK antagonists are themselves useful in treating CCK-related disorders of the appetite regu-
 35 latory systems of animals as well as in potentiating and prolonging opiate-mediated analgesia, thus having utility
 in the treatment of pain [see P. L. Faris et al., Science 226, 1215 (1984)], while selective gastrin antagonists
 are useful in the modulation of CNS behavior, as a palliative for gastrointestinal neoplasms, and in the treatment
 and prevention of gastrin-related disorders of the gastrointestinal system in humans and animals, such as peptic
 40 ulcers, Zollinger-Ellison syndrome, antral G cell hyperplasia and other conditions in which reduced gastrin
 activity is of therapeutic value. See e.g. U.S. Patent 4,820,834.

Since CCK and gastrin also have trophic effects on certain tumors [K. Okyama, Hokkaido J. Med. Sci. 60,
 206-216 (1985)], antagonists of CCK and gastrin are useful in treating these tumors [see, R.D. Beauchamp et
 al., Ann. Surg., 202, 303 (1985)].

Four distinct chemical classes of CCK-receptor antagonists have been reported [R. Freidinger, Med. Res.
 45 Rev. 9, 271 (1989)]. The first class comprises derivatives of cyclic nucleotides, of which dibutyryl cyclic GMP
 has been shown to be the most potent by detailed structure-function studies (see, N. Barlas et al., Am. J.
Physiol. 242, G 161 (1982) and P. Robberecht et al., Mol. Pharmacol., 17, 268 (1980)).

The second class comprises peptide antagonists which are C-terminal fragments and analogs of CCK, of
 50 which both shorter (Boc-Met-Asp-Phe-NH₂, Met-Asp-Phe-NH₂), and longer (Cbz-Tyr(SO₃H)-Met-Gly-Trp-Met-
 Asp-NH₂) C-terminal fragments of CCK can function as CCK antagonists, according to recent structure-function
 studies (see, R. T. Jensen et al., Biochem. Biophys. Acta. 757, 250 (1983), and M. Spanarkel et al., J. Biol.
Chem. 258, 6746 (1983)). The latter compound was recently reported to be a partial agonist [see, J. M. Howard
 et al., Gastroenterology 86 (5) Part 2, 1118 (1984)].

Then, the third class of CCK-receptor antagonists comprises the amino acid derivatives : proglumide, a
 55 derivative of glutaric acid, and the N-acyl tryptophans including para-chlorobenzoyl-L-tryptophan (benzot-

ript), [see, W. F. Hahne et al., *Proc. Natl. Acad. Sci. U.S.A.*, **78**, 6304 (1981), R. T. Jensen et al., *Biochem. Biophys. Acta.*, **761**, 269 (1983)]. All of these compounds, however, are relatively weak antagonists of CCK (IC₅₀ : generally 10⁻⁴ M [although more potent analogs of proglumide have been recently reported in F. Makovec et al., *Arzneim-Forsch Drug Res.*, **35** (II), 1048 (1985) and in German Patent Application DE 3522506A1], but down to 10⁻⁶ M in the case of peptides), and the peptide CCK-antagonists have substantial stability and absorption problems.

In addition, a fourth class consists of improved CCK-antagonists comprising a nonpeptide of novel structure from fermentation sources [R. S. L. Chang et al., *Science*, **230**, 177-179 (1985)] and 3-substituted benzodiazepines based on this structure [published European Patent Applications 167 919, 167 920 and 169 392, B. E. Evans et al., *Proc. Natl. Acad. Sci. U.S.A.*, **83**, p. 4918-4922 (1986) and R.S.L. Chang et al., *ibid.*, p. 4923-4926] have also been reported.

No really effective receptor antagonists of the *in vivo* effects of gastrin have been reported (J. S. Morley, *Gut Pept. Ulcer Proc.*, Hiroshima Symp. 2nd, 1983, p. 1), and very weak *in vitro* antagonists, such as proglumide and certain peptides have been described [(J. Martinez, *J. Med. Chem.*, **27**, 1597 (1984)]. Recently, however, pseudopeptide analogs of tetragastrin have been reported to be more effective gastrin antagonists than previous agents [J. Martinez et al., *J. Med. Chem.*, **28**, 1874-1879 (1985)].

The benzodiazepine (BZD) structure class, which has been widely exploited as therapeutic agents, especially as central nervous system (CNS) drugs, such as anxiolytics, and which exhibits strong binding to "benzodiazepine receptors" *in vitro*, has not in the past been reported to bind to CCK or gastrin receptors. Benzodiazepines have been shown to antagonize CCK-induced activation of rat hippocampal neurones but this effect is mediated by the benzodiazepine receptor, not the CCK receptor [see J. Bradwejn et al., *Nature*, **312**, 363 (1984)]. Benzodiazepines unsubstituted at the 3-position of the seven membered ring have been shown to antagonize the effects of CCK-4 (a CCK analog) [See DeMontigny, C. *Arch. Gen. Psychiatry*, **46**, 511 (1989)]. Of the reported BZD's, additionally, the large majority do not contain substituents attached to the 3-position of the seven membered ring, as it is well known in the art that 3-substituents result in decreasing benzodiazepine receptor affinity and decreasing anxiolytic activity, especially as these substituents increase in size.

Contrary to these findings, applicants have discovered a class of benzodiazepines with 3-substituents having high CCK and/or gastrin receptor affinity and low benzodiazepine receptor affinity. The compounds of the present invention also provide enhanced aqueous solubility as compared to those of U.S. 4,820,834. The compounds of the invention are useful in the treatment of disorders of gastric secretion, appetite regulation, gastrointestinal motility, pancreatic secretion, and dopaminergic function, as well as in treatment of producing potentiation of morphine and other opiate analgesias. The present compounds also provide improvements in aqueous solubility, receptor selectivity, oral bioavailability, and duration of action.

It is, therefore, an object of this invention to identify substances which more effectively antagonize or inhibit the function of cholecystokinins and gastrin in the treatment of disorders of gastric secretion, appetite regulation, gastrointestinal motility, pancreatic secretion, and dopaminergic function, as well as in treatment or producing potentiation of morphine and other opiate analgesias. It is another object of this invention to develop a method of antagonizing the functions of cholecystokinin and/or gastrin in these disorders. It is also an object of this invention to develop a method of preventing or treating these disorders.

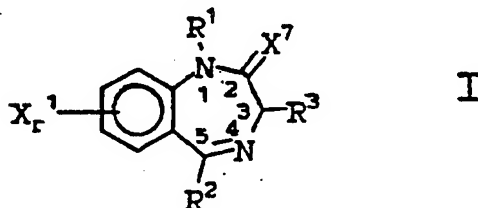
The substituted benzodiazepines of the present invention are also useful for directly inducing analgesia, either opiate mediated or non-opiate mediated. Furthermore, the compounds of the present invention are useful as anesthetic agents involving the loss of pain sensations. It is therefore another object of the present invention to identify substances which more effectively antagonize or inhibit the function of CCK or gastrin for the purpose of effecting analgesia, anesthesia, or loss of pain sensation. Yet another object of the present invention is to develop methods of antagonizing or inhibiting the functions of CCK or gastrin for the purpose of effecting analgesia, anesthesia or loss of pain sensation.

SUMMARY OF THE INVENTION

It has now been found that compounds of Formula I are antagonists of gastrin and cholecystokinin (CCK) and bind to the gastrin and CCK receptors. Pharmaceutical compositions containing effective amounts of these compounds are useful in the treatment and prevention of CCK and/or gastrin-related disorders of gastric secretion, appetite regulation, gastrointestinal motility, pancreatic secretion, and dopaminergic function, as well as in treatment producing potentiation of morphine and other opiate analgesics. The present compounds provide enhanced aqueous solubility.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of formula I are useful in a method of antagonizing the binding of cholecystokinin to cholecystokinin receptors or antagonizing the binding of gastrin to gastrin receptors which comprises contacting said cholecystokinin receptors or said gastrin receptors, respectively, with a compound represented by the formula :

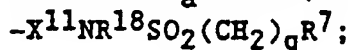
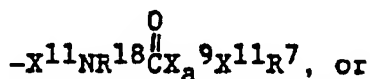
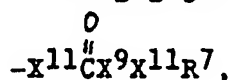
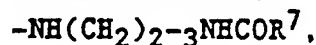
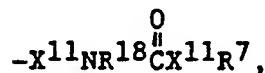


wherein :

R¹ is H, C₁-C₆ linear or branched alkyl, loweralkenyl, lower alkynyl, X¹²COOH, -X¹²COOR⁶, -X¹¹-cycloalkyl, -X¹²NR⁴R⁵, -X¹²CONR⁴R⁵, -X¹²CN, or -X¹¹CX₃¹⁰ ;

R² is H, loweralkyl, substituted or unsubstituted phenyl (wherein the substituents may be 1 or 2 of halo, loweralkyl, loweralkoxy, loweralkythio, carboxyl, carboxyloweralkyl, nitro, -CF₃, or hydroxy), 2-, 3-, or 4-pyridyl ;

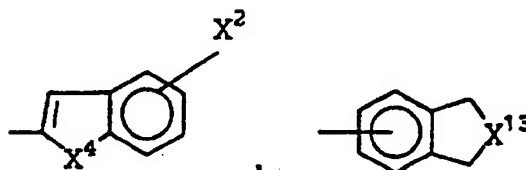
R³ is



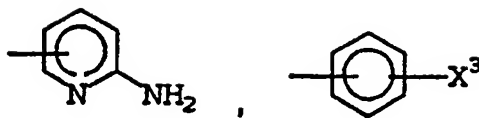
R⁴ and R⁵ are independently H or R⁶ or in combination with the N of the NR⁴R⁵ group form an unsubstituted or mono or disubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring, or benzofused, 4-7 membered heterocyclic ring wherein said heterocyclic ring or said benzofused heterocyclic ring may contain a second heteroatom selected from O and NCH₃ and the substituents(s) is/are independently selected from C₁-C₄alkyl ;

R⁶ is loweralkyl, cycloweralkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted phenyloweralkyl wherein the phenyl or phenyloweralkyl substituents may be 1 or 2 of halo, loweralkyl, loweralkoxy, nitro, or CF₃ ;

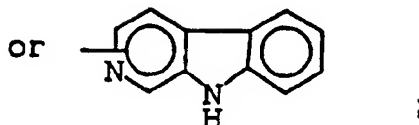
R⁷ is



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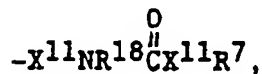
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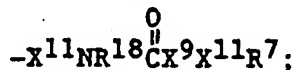
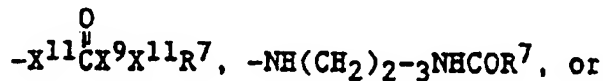
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- R^8 is H, loweralkyl, cycloloweralkyl, $-X^{13}CONH_2$, $-X^{13}COOR^6$, $-X^{13}COOH$, $-X^{13}$ -cycloloweralkyl, or $-X^{13}NR^4R^5$;
- 20 R^{15} is H, or loweralkyl;
- R^{18} is H or loweralkyl;
- n is 1-6;
- q is 0-4;
- r is 1 or 2;
- 25 X^1 is H, $-NO_2$, CF_3 , CN, OH, loweralkyl, halo, loweralkylthio, loweralkoxy, $-X^{11}COOR^6$, $X^{11}COOH$, or $-X^{11}NR^4R^5$;
- X^2 is H or X^3 , with the proviso that when X^2 is H, then X^4 is NX^5COOH or NX^5COOR^6 wherein X^5 is a linear alkyl chain of 2 to 6 carbon atoms, any carbon atom of which may be additionally substituted with a linear or branched alkyl group of 1 to 3 carbon atoms;
- 30 X^3 is $O(CH_2)_nCOOR^6$, $O(CH_2)_nCOOH$, $(CH_2)_nCOOR^6$, $(CH_2)_nCOOH$, $COOR^6$, or $X^{12}OR^6$;
- X^4 is S, O, CH_2 , or NR^8 ;
- X^7 is O, S, HH, or NR^{15} with the proviso that X^7 can be NR^{15} only when R^1 is not H;
- X^8 is H, loweralkyl;
- X^9 and X_{10} are independently NR^{18} or O;
- 35 X^{10} is F, Cl, or Br;
- X^{11} is absent or C_{1-4} linear or branched alkyl;
- X^{12} is C_{1-4} linear or branched alkylidene;
- X^{13} is C_{1-4} linear or branched alkyl;
- or pharmaceutically acceptable salts thereof.
- 40 One embodiment of the present invention encompasses compounds of formula 1, wherein:
- R^1 is H, C_1 - C_6 linear or branched alkyl, $-X^{12}COOR^6$, $-X^{11}$ -cycloloweralkyl, $X^{12}NR^4R^5$, $-X^{12}CONR^4R^5$, or $X^{12}COOH$;
- R^2 is substituted or unsubstituted phenyl (wherein the substituents may be 1 or 2 of halo, loweralkyl, loweralkoxy, loweralkylthio, carboxyl, carboxyloweralkyl, nitro, $-CF_3$ or hydroxy), 2-, 3-, or 4-pyridyl;
- 45 R^3 is

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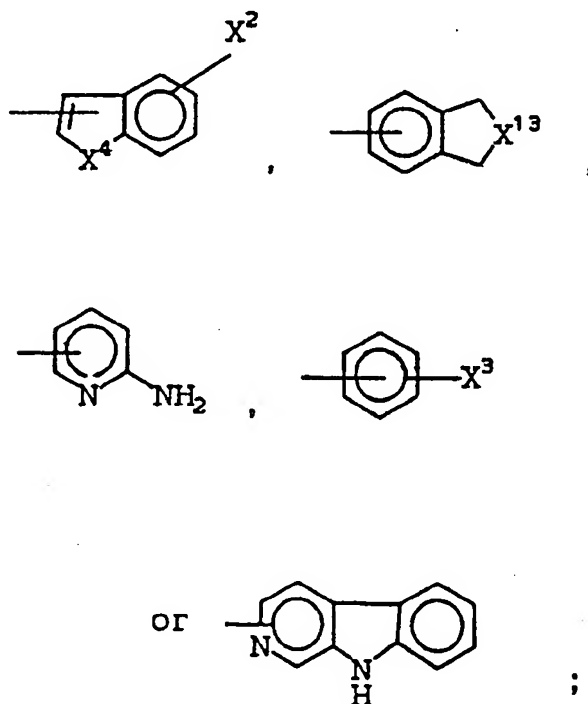


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R^4 and R^5 are independently H or R^6 or in combination with the N or the NR^4R^5 group form an unsubstituted or mono or disubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring, or benzofused 4-7 membered heterocyclic ring wherein said heterocyclic ring or said benzofused heterocyclic ring may contain a second heteroatom selected from O and NCH_3 and the substituents(s) is/are independently selected from C_1 - C_4 alkyl ;

R^6 is C_{1-4} straight or branched-chain alkyl or C_3 - C_6 cycloalkyl ;
 R^7 is



R^8 is H, loweralkyl, cycloloweralkyl, $X^{13}COOR^6$, $X^{13}COOH$, or $X^{13}NR^4R^5$;
 R^{18} is H or loweralkyl ;
 n is 1-3 ;
 q is 0-3 ;
 r is 1 or 2 ;
 X^1 is H, $-NO_2$, CF_3 , CN, loweralkyl, halo, loweralkylthio, $-X^{11}COOR^6$, $X^{11}COOH$, or $X^{11}NR^4R^5$;
 X^2 is H or X^3 with the proviso that when X^2 is H, then X^4 is NX^5COOH or NX^5COOR^6 wherein X^5 is a linear alkyl chain of 2 to 4 carbon atoms, any carbon atom of which may be additionally substituted with a linear or branched alkyl group of 1 to 3 carbon atoms ;
 X^3 is $O(CH_2)_nCOOR^6$, $O(CH_2)_nCOOH$, $(CH_2)_nCOOR^6$, $(CH_2)_nCOOH$, or $COOR^6$;
 X^4 is S, O, or NR^8 ;
 X^7 is O ;
 X^9 and X_a^9 are independently NR^{18} , or O ;
 X^{11} is absent or C_{1-4} linear alkyl ;
 X^{12} is C_{1-4} linear or branched alkylidene ;
 X^{13} is C_{1-4} linear or branched alkyl ;
or pharmaceutically acceptable salt thereof.

As used herein, the definition of each substituent e.g., R^7 , loweralkyl, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure. Alkylidene is an alkyl group with two hydrogens abstracted from the same carbon atoms.

As used herein, halo is F, Cl, Br or I ; alkyl and loweralkyl are each, unless otherwise indicated, 1-7 carbon

straight or branched chain saturated alkyl having one or sometimes two hydrogens abstracted, and includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and t-butyl, pentyl, hexyl, and heptyl; in loweralkoxy and loweralkylthio, the alkyl portion is loweralkyl as previously defined; cycloloweralkyl is cycloalkyl of 3-7 carbons; loweralkenyl is 1-5 carbon straight or branched chain alkenyl; acyl is formyl, acetyl, propionyl, benzoyl or butyryl; loweralkynyl is 1-5 carbon straight or branched chain alkynyl.

The pharmaceutically acceptable salts of the compounds of Formula I include the conventional non-toxic salts or the quarternary ammonium salts of the compounds of Formula I formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of Formula I which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

The pharmaceutically acceptable salts of the acids of Formula I are also readily prepared by conventional procedures such as treating an acid of Formula I with an appropriate amount of a base, such as an alkali or alkaline earth metal hydroxide e.g. sodium, potassium, lithium, calcium, or magnesium, or an organic base such as an amine, e.g., dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like, or a quaternary ammonium hydroxide such as tetramethylammonium hydroxide and the like.

The compounds of Formula I antagonize CCK and/or gastrin and are useful as pharmaceutical agents for mammals, especially for humans, in the treatment or prevention of disorders involving anxiety and other panic type disorders, gastric secretion, appetite regulation, gastrointestinal motility, pancreatic secretion, and dopaminergic function, as well as in treatment producing potentiation of morphine and other opiate analgesics. Examples of such disorders include panic disorders, panic syndrome, anticipatory anxiety, phobic anxiety, panic anxiety, chronic anxiety, and endogenous anxiety, gastrointestinal disorders, especially such as irritable bowel syndrome, gastroesophageal reflux disease or ulcers, excess pancreatic or gastric secretion, acute pancreatitis, or motility disorders; central nervous system disorders, caused by CCK interactions with dopamine, such as neuroleptic disorders, tardive dyskinesia, Parkinson's disease, psychosis or Gilles de la Tourette Syndrome; disorders of appetite regulatory systems; Zollinger-Ellison syndrome, antral G cell hyperplasia, or pain (potentiation of opiate analgesia); as well as certain tumors of the lower esophagus, stomach, intestines and colon. The compounds of formula I are also useful for directly inducing analgesia, which includes opiate and non-opiate mediated analgesia, as well as anesthesia or loss of the sensation of pain.

The present invention also encompasses a pharmaceutical composition useful in the treatment of these disorders or other disorders involving CCK and/or gastrin antagonism, comprising an effective amount of a CCK and/or gastrin antagonist of formula I, with or without pharmaceutically-acceptable carriers or diluents. In addition, the present invention encompasses a pharmaceutical composition useful for directly inducing analgesia, anesthesia or loss of the sensation of pain.

The compounds of Formula I thereof, may be administered to a human subject either alone or, preferably, in combination with pharmaceutically-acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including intravenous, intramuscular, intraperitoneal, subcutaneous and topical administration.

For oral use of an antagonist of CCK, according to this invention, the selected compounds may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

When a compound according to Formula I is used as an antagonist of CCK or gastrin in a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms. However, in most instances, an effective daily dosage will be in the range of from about 0.05 µg/kg

to about 50 mg/kg of body weight, and preferably, of from 0.5 µg/kg to about 20 mg/kg of body weight, administered in single or divided doses. In some cases, however, it may be necessary to use dosages outside these limits.

In the treatment of irritable bowel syndrome, for instance, 0.1 to 10 mg/kg or a CCK antagonist might be administered orally (p.o.), divided into two doses per day (b.i.d.). In treating delayed gastric emptying, the dosage range would probably be the same, although the drug might be administered either intravenously (I.V.) or orally, with the I.V. dose probably tending to be slightly lower due to better availability. Acute pancreatitis might be treated preferentially in an I.V. form, whereas spasm and/or reflex esophageal, chronic pancreatitis, post vagotomy diarrhea, anorexia or pain associated with biliary dyskinesia might indicate p.o. form administration.

In the use of a gastrin antagonist as a tumor palliative for gastrointestinal neoplasms with gastrin receptors, as a modulator of central nervous system activity, treatment of Zollinger-Ellison syndrome, or in the treatment of peptic ulcer disease, a dosage of 0.1 to 10 mg/kg administered one-to-four times daily might be indicated.

Because these compounds antagonize the function of CCK in animals, they may also be used as feed additives to increase the food intake of animals in daily dosage of approximately 0.05 to 100 µg/kg of body weight.

The compounds of Formula I are prepared according to the schemes and descriptions of U.S. Patent 4,820,834 herein incorporated by reference for these purposes. One preferred synthetic scheme is Scheme IVa involving nitrosation, reduction and acylation, according to U.S. Patent 4,820,834. See also Examples 1-5 below.

1. CCK Receptor Binding (Pancreas)

CCK-33 was radiolabeled with ¹²⁵I-Bolton Hunter reagent (2000 Ci/mole) as described by Sankara et al. (J. Biol. Chem. 254 : 9349-9351, 1979). Receptor binding was performed according to Innis and Snyder (Proc. Natl. Acad. Sci. 77, 6917-6921, 1980) with the minor modification of adding the additional protease inhibitors, phenylmethane sulfonyl fluoride and o-phenanthroline. The latter two compounds have no effect on the ¹²⁵I-CCK receptor binding assay.

Male Sprague-Dawley rats (200-350 g) were sacrificed by decapitation. The whole pancreas was dissected free of fat tissue and was homogenized in 20 volumes of ice-cold 50 mM, Tris HCl (pH 7.7 at 25°C) with a Brinkmann Polytron PT 10. The homogenates were centrifuged at 48,000 g for 10 min. Pellets were resuspended in Tris Buffer, centrifuged as above and resuspended in 200 volumes of binding assay buffer (50 mM Tris HCl, pH 7.7 at 25°C, 5 mM dithiothreitol, 0.1 mM bacitracin, 1.2 mM phenylmethane sulfonyl fluoride and 0.5 mM o-phenanthroline). For the binding assay, 25 µl of buffer (for total binding) or unlabeled CCK-8 sulfate to give a final concentration of 1 µM (for nonspecific binding) or the compounds of Formula I (for determination of inhibition of ¹²⁵I-CCK binding) and 25 µl of ¹²⁵I-CCK-33 (30,000-40,000 cpm) were added to 450 µl of the membrane suspensions in microfuge tubes. All assays were run in duplicate or triplicate. The reaction mixtures were incubated at 37°C for 30 minutes and centrifuged in a Beckman Microfuge (4 minutes) immediately after adding 1 ml of ice-cold incubation buffer. The supernatant was aspirated and discarded, pellets were counted with a Beckman gamma 5000. For Scatchard analysis (Ann. N.Y. Acad. Sci. 51 : 660, 1949), ¹²⁵I-CCK-33 was progressively diluted with increasing concentrations of CCK-33.

2. CCK Receptor Binding (Brain)

CCK-33 was radiolabeled and the binding was performed according to the description for the pancreas method with modifications according to Saito et al., J. Neurochem. 37 : 483-490, 1981.

Male Hartley guinea pigs (300-500 g) were sacrificed by decapitation and the brains were removed and placed in ice-cold 50 mM, Tris HCl plus 7.58 g/l Trizma-7.4 (pH 7.4 at 25°C). Cerebral cortex was dissected and used as a receptor source. Each gram of fresh guinea pig brain tissue was homogenized in 10 ml of Tris/Trizma buffer with a Brinkman polytron PT-10. The homogenates were centrifuged at 42,000 g for 15 minutes. Pellets were resuspended in Tris Buffer, centrifuged as above and resuspended in 200 volumes of binding assay buffer (10 mM N-2-hydroxyethyl-piperazine-N'-2-ethane sulfonic acid (HEPES), 5 mM MgCl₂, 0.25 mg/ml bacitracin, 1 mM ethylene glycol-bis-(β-aminoethyl ether-N,N'-tetraacetic acid) (EGTA), and 0.4% bovine serum albumin (BSA)). For the binding assay, 25 µl of buffer (for total binding) or unlabeled CCK-8 sulfate to give a final concentration of 1 µM (for nonspecific binding) or the compounds of Formula I (for determination of inhibition of ¹²⁵I-CCK binding) and 25 µl of ¹²⁵I-CCK-33 (30,000-40,000 cpm) were added to 450 µl of the membrane suspensions in microfuge tubes. All assays were run in duplicate or triplicate. The reaction mixtures were incubated at 25°C for 2 hours and centrifuged in a Beckman Microfuge (4 minutes) immediately after adding 1 ml of ice-cold incubation buffer. The supernatant was aspirated and discarded, pellets were counted with a Beckman gamma 5000.

The compounds of Formula I can be determined to be competitive antagonists of CCK according to the following assays.

3. Isolated guinea pig gall bladder

5

Male Hartley guinea pigs (400-600 g) are sacrificed by decapitation. The whole gall bladder is dissected free from adjacent tissues and cut into two equal halves. The gall bladder strips are suspended along the axis of the bile duct in a 5 ml organ bath under 1 g tension. The organ bath contains a Krebs bicarbonate solution (NaCl 118 mM, KCl 4.75 mM, CaCl₂ 2.54 mM, KH₂PO₄ 1.19 mM, Mg SO₄ 1.2 mM, NaHCO₃ 25 mM and dextrose 11 mM) maintained at 32°C and bubbled with 95% O₂ and 5% CO₂. Isometric contractions are recorded using Statham (60 g ; 0.12 mm) strain gauges and a Hewlett-Packard (77588) recorder. The tissues are washed every 10 minutes for 1 hour to obtain equilibrium prior to the beginning of the study. CCK-8 is added cumulatively to the baths and EC₅₀'s determined using regression analysis. After washout (every 10 minutes for 1 hour), the compound of Formula I is added at least 5 minutes before the addition of CCK-8 and the EC₅₀ of CCK-8 in the presence of the compound of Formula I similarly determined.

4. Isolated longitudinal muscle of guinea pig ileum

Longitudinal muscle strips with attached nerve plexus are prepared as described in *Brit. J. Pharmac.* 23 : 356-363, 1964 ; *J. Physiol.* 194 : 13-33, 1969. Male Hartley guinea pigs are decapitated and the ileum removed (10 cm of the terminal ileum is discarded and the adjacent 20 cm piece used). A piece (10 cm) of the ileum is stretched on a glass pipette. Using a cotton applicator to stroke tangentially away from the mesentery attachment at one end, the longitudinal muscle is separated from the underlying circular muscle. The longitudinal muscle is then tied to a thread and by gently pulling, stripped away from the entire muscle. A piece of approximately 2 cm is suspended in 5 ml organ bath containing Krebs solution and bubbled with 95% O₂ and 5% CO₂ at 37°C under 0.5 g tension. CCK-8 is added cumulatively to the baths and EC₅₀ values in the presence and absence of compounds of Formula I determined as described in the gall bladder protocol (above).

5. Gastrin Antagonism

30

Gastrin antagonist activity of compounds of Formula I is determined using the following assay.

A. Gastrin Receptor Binding in Guinea Pig Gastric Glands

35 Preparation of guinea pig gastric mucosal glands

Guinea pig gastric mucosal glands were prepared by the procedure of Bergling and Obrink *Acta Physiol. Scand.* 98 : 150 (1976) with a slight modification according to Praissman *et al.* *C. J. Receptor Res.* 3 : (1983). Gastric mucosa from guinea pigs (300-500 g body weight, male Hartley) were washed thoroughly and minced with fine scissors in standard buffer consisting of the following : 130 mM NaCl, 12 mM NaHCO₃, 3 mM NaH₂PO₄, 3 mM Na₂HPO₄, 3 mM K₂HPO₄, 2 mM MgSO₄, 1mM CaCl₂, 5 mM glucose and 4 mM L-glutamine, 25 mM HEPES at pH 7.4. The minced tissues were washed and then incubated in a 37°C shaker bath for 40 minutes with the buffer containing 0.1% collagenase and 0.1% BSA and bubbled with 95% O₂ and 5% CO₂. The tissues were passed twice through a 5 ml glass syringe to liberate the gastric glands, and then filtered through 200 mesh nylon. The filtered glands were centrifuged at 270 g for 5 minutes and washed twice by resuspension and centrifugation.

B. Binding studies

The washed guinea pig gastric glands prepared as above were resuspended in 25 ml of standard buffer containing 0.25 mg/ml of bacitracin. For binding studies, to 220 µl of gastric glands in triplicate tubes, 10 µl of buffer (for total binding) or gastrin (1 µM final concentration, for nonspecific binding) or test compound and 10 µl of ¹²⁵I-gastrin (NEN, 2200 Ci/mmol, 25 pM final) or ³H-pentagastrin (NEN 22 Ci/mmol, 1 nM final) were added. The tubes were aerated with 95% O₂ and 5% CO₂ and capped. The reaction mixtures after incubation at 25°C for 30 minutes were filtered under reduced pressure on glass G/F B filters (Whatman) and immediately washed further with 4 x 4 ml of standard buffer containing 0.1% BSA. The radioactivity on the filters was measured using a Beckman gamma 5500 for ¹²⁵I-gastrin or liquid scintillation counting for ³H-pentagastrin.

In Vitro ResultsEffect of The Compounds of Formula I on ^{125}I -CCK-33 receptor binding

The preferred compounds of Formula I are those which inhibited specific ^{125}I -CCK-33 binding in a concentration dependent manner.

Scatchard analysis of specific ^{125}I -CCK-33 receptor binding in the absence and presence of the compounds of Formula I indicated the compound of Formula I competitively inhibited specific ^{125}I -CCK-33 receptor binding since it increased the K_D (dissociation constant) without affecting the B_{max} (maximum receptor number).

A K_i value (dissociation constant of inhibitor) of the compounds of Formula I was estimated.

The data of Table I were obtained for compounds of Formula I.

TABLE I
CCK RECEPTOR BINDING RESULTS
 $\text{IC}_{50}(\mu\text{M})$

Compound of EX#	^{125}I -CCK Pancreas	^{125}I -CCK Brain	^{125}I -Gastrin
			Gastric Glands
5	0.28	0.002	0.0011
6	0.00013	0.1290	0.07000
7	0.00010	0.2300	0.24000
9	0.04900	0.0039	0.00900
10	0.04900	0.0039	0.00900
12	0.00240	0.1600	0.24000
13	0.01400	0.0710	6.40000
14	2.70000	0.0110	0.40000
15	0.00330	0.9100	
16	0.02300	0.1600	
17	0.06900	0.0120	0.00380
18	2.6	0.024	0.01
19	0.02	0.026	0.018

EXAMPLE 11,3-Dihydro-1-methyl-3-oximino-5-phenyl(-2H-1,4-benzodiazepin-2-one

To a suspension of potassium *tert*-butoxide (24.9 g, 222 mmole) in 600 ml of dry tetrahydrofuran was added 200 ml of dry *tert*-butylalcohol at -20°C under nitrogen. To this solution was then added via addition funnel 1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (25 g, 99.9 mmole) in 260 ml of tetrahydrofuran. The resulting wine colored solution was stirred for 2 hours at -20°C and treated with 17.4 ml (130 mmole) of isoamyl nitrite. The reaction mixture was warmed to 0°C over 15 minutes and quenched with the addition of 60 ml of cold water and 20 ml of glacial acetic acid. All solvents were removed under reduced pressure and the residue was partitioned between ethyl acetate (600 ml) and brine (100 ml). The phases were separated and the organic extracts were dried (Na_2SO_4) and concentrated. The resulting semi-solid was triturated with ether to give 21 g of off-white solid. m.p. $234-235^\circ\text{C}$; $R_f = 0.15$ (ethyl acetate-hexane, 1 : 1); $R_f = 0.28$ chloroform-ethanol, 95 : 5);

ir(KBr, partial): 3300, 1650, 1595, 1320, 1205, 1030, 975 cm^{-1} .

MS (14 ev.) : 279 (M⁺), 262, 249, 236, 222.

¹HNMR (CDCl₃) : confirms structure assignment.

Elemental Analysis Calc'd for C₁₆H₁₃N₃O₂ :

5 C, 4.69 ; H, 68.81 ; N, 15.04.

Found : C, 4.62 ; H, 68.67 ; N, 15.08.

EXAMPLE 2

10 3(R,S)-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

A solution of 150 ml of methanol containing 5 g (17.9 mmole) of 1,3-dihydro-1-methyl-3-oximino-5-phenyl-1,4-benzodiazepin-2-one was treated with a slurry of active Raney-nickel catalyst¹ in ethanol (10 g wet weight). The resulting suspension was hydrogenated on a Parr apparatus at 60 psi and 23°C for 30 hours. The catalyst was removed by filtration and the filtrate was concentrated to afford the title compound in 95% yield.

15 R_f = 0.23 (chloroform-ethanol, 95 : 5), R_f = 0.23 (chloroform-methanol-acetic acid-water, 90 : 10 : 1 : 1) ¹HNMR (CDCl₃) : spectrum confirms structure assignment.

1 Raney-Nickel catalyst was prepared according to Fieser & Fieser, Reagents for Organic Synthesis, Vol. I, John Wiley & Sons, Inc., New York 1967, p. 729.

20 EXAMPLE 3

3(S)-(-)-1,3-Dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

3(S)-(-)-3-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (595 mg, 2.24 mmole) was dissolved in CH₂Cl₂ (15 ml) and treated with 2-indolecarbonyl chloride (403 mg, 2.24 mmole) followed by triethylamine (227 mg, 2.24 mmole). The mixture was stirred at room temperature for 30 minutes and concentrated in vacuo. The residue was chromatographed on silica gel (5% Et₂O/CH₂Cl₂) and the combined product fractions evaporated to dryness in vacuo. Three times, Et₂O (15 ml) was added and evaporated in vacuo to give the title compound : (m.p. 168°-185°C).

TLC : Silica gel (6% Et₂O/CH₂Cl₂), R_f = 0.23

30 NMR : Consistent with structure

HPLC : Greater than 99% pure.

M.S. : Molecular ion at m/e = 408

[α]_D²⁵ = -103° (0.0078 g/ml, CH₂Cl₂)

Anal. calc'd for C₂₅H₂₀N₄O₂ :

35 C, 73.51 ; H, 4.94 ; N, 13.72 ;

Found : C, 73.38 ; H, 4.80 ; N, 13.66.

EXAMPLE 4

40 3(RS)-(Boc-L-tryptophanyl)amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

3-(RS)-Amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (0.1 g, 0.4 mmol), BOC-L-tryptophan (0.12 g, 0.4 mmol), and DCC (0.4 ml of a 1 M solution in CH₂Cl₂, 0.4 mmol) were combined in 2 ml of THF to which were added 2 ml of DMF and 2 ml of CH₂Cl₂. The mixture was treated with triethylamine (0.11 ml), stoppered, and stirred at room temperature for four days. The mixture was treated with citric acid solution (10%, 3 ml) and CH₂Cl₂ (5 ml), shaken and separated. The aqueous phase was extracted with CH₂Cl₂ (2 × 5 ml). The combined organic layers were washed with citric acid (10%, 2 × 5 ml), sodium bicarbonate (10%, 2 × 5 ml), and H₂O (10 ml), dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel (1 : 1 (v/v) Et₂O/CH₂Cl₂) and the combined product fractions evaporated to dryness in vacuo. The residue was triturated with petroleum ether and the solid dried in vacuo at 70° : (m.p. 173-177°C (↑)).

TLC : Single spot (R_f = 0.56, silica gel plate, 10% (v/v) CH₃OH in CH₂Cl₂).

NMR : The spectrum was consistent with the title structure and verified the presence of two diastereomers.

HPLC : Greater than 99.7% pure (36% and 63.7%).

55 MS (FAB) : a molecular ion at m/e = 537.

Anal. calc'd for C₃₁H₃₁N₅O₄ :

C, 69.25 ; H, 5.81 ; N, 13.03 ;

Found : C, 69.48 ; H, 6.18 ; N, 12.96.

EXAMPLE 5

5 (R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)-urea

Equimolar amounts of 3(R)-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and 3-methylphenylisocyanate were mixed in 8 ml of dry tetrahydrofuran at room temperature. The reaction mixture was allowed to stand for 8 hours and was then filtered. The collected solids were washed with tetrahydrofuran and dried *in vacuo* over P₂O₅ to give analytical product : m.p. 208-210°C.

10 NMR : Confirms structure assignment of product.

HPLC : Greater than 99% pure.

MS : Molecular ion at m/e = 399 (M + H) (FAB).

Anal. Calc'd for C₂₄H₂₂N₄O₂ :

15 C, 72.34 ; H, 5.56 ; N, 14.06.

Found : C, 72.12 ; H, 5.84 ; N, 14.04.

EXAMPLE 6

20 3(S)-3-(2-(N-carboxymethylindole)carbonylamino)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

Sodium hydride (0.034 g, 0.71 mmole of a 50% dispersion in mineral oil) and 3(S)-(-)-1,3-Dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (0.28 g, 0.69 mmole) were combined in dry, degassed DMF (5 ml) and stirred in an ice bath for 40 minutes. Ethyl bromoacetate (0.077 ml, 0.115 g, 0.69 mmole) was added in one portion, and the mixture stirred one hour at room temperature. The DMF was removed *in vacuo*, and the residue treated with cold, aqueous sodium bicarbonate solution and extracted with ethyl acetate. The ethyl acetate fractions were combined, washed with water, dried over sodium sulfate, filtered, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel eluted with 7% ether in CH₂Cl₂. The product fractions were combined and evaporated to dryness *in vacuo*. The residue (0.25 g, 0.53 mmole) was stirred in CH₃OH (5 ml) and treated with aqueous sodium hydroxide (0.7 ml of a 1 N solution ; 0.7 mmole). The mixture was stirred overnight at room temperature, then acidified with 1 N HCl and extracted with ethyl acetate. The ethyl acetate fractions were combined, dried over sodium sulfate, filtered, and evaporated to dryness *in vacuo*. The residue was crystallized from a mixture of acetone, ether, and petroleum ether to give the title compound : (m.p. 165-195°C (indistinct)).

35 TLC : Silica gel (90 : 10 : 1 : 1, CH₂Cl₂ : CH₃OH : HOAc : H₂O), R_f = 0.52

NMR : Consistent with structure

HPLC : Greater than 97% pure

M.S. : Molecular ion at M + H = 467 (FAB).

Anal. calc'd for C₂₇H₂₂N₄O₄·0.15 C₄H₁₀O·0.45 H₂O

40

C, 68.24 ; H, 5.06 ; N, 11.54 ;

Found : C, 68.21 ; H, 4.85 ; N, 11.47.

EXAMPLE 7

45

(S)-4-[2-(((2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)amino)carbonyl)-1H-indolyl-1]-butanoic acid

Sodium hydride (0.1 g, 2.5 mmole of a 60% dispersion in mineral oil) and 3(S)-(-)-1,3-dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (1.0 g, 2.45 mmole) were combined in dry, degassed DMF (10 ml) and stirred in an ice bath for 40 minutes. Ethyl-4-bromobutyrate (0.52 g, 2.7 mmole) was added in one portion, and the mixture stirred three hours at room temperature. The DMF was removed *in vacuo*, and the residue was treated with CH₃OH (350 ml) and aqueous 1 N NaOH (10 ml) and stirred at room temperature for three days. The mixture was evaporated to dryness *in vacuo*, and the residue was treated with aqueous sodium bicarbonate solution and extracted with ethyl acetate. The aqueous fraction was made acidic with 1N HCl and extracted with ethyl acetate. The ethyl acetate layer was dried over sodium sulfate and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel (7% Et₂O/CH₂Cl₂ followed by 540: 10 : 1 : 1, CH₂Cl₂ :

55

CH₃OH : HOAc : H₂O, and the product fractions evaporated to dryness *in vacuo*. The residue was crystallized

from ether to give the title compound : (m.p. 192-195°C).

TLC : Silica gel (90 : 10 : 1 : 1, CH₂Cl₂ : CH₃OH : HOAc : H₂O), R_f = 0.23

NMR : Consistent with structure

HPLC : Greater than 97% pure

5 M.S. : Molecular ion at M + H = 495 (FAB)

Anal. calc'd for C₂₉H₂₆N₄O₄

C, 70.43 ; H, 5.30 ; N, 11.33 ;

Found : C, 70.14 ; H, 5.42 ; N, 11.36.

10

EXAMPLE 8

(RS)-1,3-Dihydro-1-methyl-3-(p-nitrophenyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one

3-(RS)-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (15.1 g, 57 mmole) was dissolved in THF (150 ml), cooled in an ice bath, and treated with triethylamine (7.93 ml). A solution of p-nitrophenylchloroformate (11.45 g, 57 mmole) in THF (70 ml) was added dropwise. An additional 1 ml of triethylamine and a solution of 2.0 g of p-nitrophenylchloroformate in THF were added. After stirring one hour, the mixture was filtered and evaporated to dryness *in vacuo*. Ether was added and the mixture stirred one hour at room temperature and filtered. The solid was washed twice with ether and dried to give the title compound.

20

EXAMPLE 9

(RS)-3-((((2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)amino)carbonyl)amino)benzoic acid, also known as (RS)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-carboxyphenyl)-urea.

25

(RS)-1,3-Dihydro-1-methyl-3-(p-nitrophenyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one (5.03 g, 11.2 mmole) and m-aminobenzoic acid (2.4 g, 17.5 mmole) were combined in DMF (120 ml), treated with triethylamine (4.2 ml), and stirred in an oil bath thermostatted at 45° for 18 hours. The DMF was removed *in vacuo* and the residue was dissolved in boiling methanol. The crystallized product was recrystallized from hot methanol : (m.p. 175-180°C).

30

TLC : Silica gel (90 : 10 : 1 : 1, CH₂Cl₂ : CH₃OH : HOAc : H₂O), R_f = 0.5

NMR : Consistent with title structure

HPLC : Greater than 97.8% pure

M.S. : M + H at m/e = 429 (FAB)

35

Anal. calc'd for C₂₄H₂₀N₄O₄·1.15H₂O

C, 64.17 ; H, 5.00 ; N, 12.47 ;

Found : C, 64.20 ; H, 5.20 ; N, 12.60.

40

EXAMPLE 10

(R)-3-((((2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)amino)carbonyl)amino)benzoic acid

45

Benzyl alcohol (10 g, 92.6 mmole) was treated with a solution of m-nitrobenzoyl chloride (17.5 g, 94.5 mmole) in ether (50 ml) added dropwise. The mixture was stirred at room temperature for eighteen hours, then washed twice with aqueous sodium bicarbonate, dried over sodium sulfate, and filtered. The filtrate was evaporated to dryness *in vacuo* and the residue chromatographed on silica gel eluted with 1 : 1 CH₂Cl₂ : hexane. The product fractions were combined and evaporated to dryness *in vacuo*. A portion (5.2 g, 20.2 mmole) of the resulting benzyl m-nitrobenzoate was dissolved in ethanol and hydrogenated over platinum oxide (70 mg) at 50 psi of H₂. The resulting mixture was filtered and evaporated to dryness *in vacuo* to give benzyl m-aminobenzoate.

50

(R)-1,3-Dihydro-1-methyl-3-(p-nitrophenyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one was prepared using the procedure of Example 8 wherein 3-(R)-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one was employed in place of the (RS) compound.

55

To benzyl m-aminobenzoate (0.25 g, 1.10 mmole) in DMF (17 ml) was added triethylamine (0.23 ml) followed by a solution of (R)-1,3-dihydro-1-methyl-3-(p-nitrophenyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one (0.469 g, 1.09 mmole) in DMF (23 ml) containing triethylamine (0.23 ml). The mixture was stirred at room temperature for one hour, then treated with water, made acidic with 1N HCl, and extracted with

ethyl acetate. The ethyl acetate layers were combined, washed with aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel eluted with 500 ml each of 5%, 6%, 7%, 9%, 10%, and 12% ether in CH₂Cl₂. The product fractions were combined and evaporated to dryness *in vacuo*. A portion of the residue (81.2 mg, 0.086 mmole) was dissolved in ethanol (70 ml) and hydrogenated over palladium/charcoal (20 mg) at 50 psi of H₂. The mixture was filtered and evaporated to dryness *in vacuo* to provide the title compound.

TLC : Silica gel (90 : 10 : 1 : 1, CH₂Cl₂ : CH₃OH : HOAc : H₂O) identical to material prepared as in example 9.

EXAMPLE 11

3-(RS)-Amino-1,3-dihydro-1-(2-hydroxyethyl)-5-phenyl-2H-1,4-benzodiazepin-2-one
1,3-Dihydro-5-phenyl-3(R,S)-[(benzyloxycarbonyl)-amino]-2H-1,4-benzodiazepin-2-one¹ (0.25 g, 0.65 mmole) was dissolved in DMF (5 ml) stirred in an ice bath. The solution was treated with sodium hydride (32.7 mg, 0.681 mmole of a 50% dispersion in mineral oil) and the mixture stirred for forty minutes in the cold. Oxirane gas was bubbled into the mixture for five minutes, and the resulting mixture heated on a steam bath for one hour. The DMF was removed *in vacuo*. The residue was treated with water and extracted with ethyl acetate. The ethyl acetate layers were combined, washed with water, dried over sodium sulfate, filtered, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel eluted with 35% ethyl acetate in methylene chloride. The combined product fractions were evaporated to dryness *in vacuo*. The residue was dissolved in CH₂Cl₂, cooled in an ice bath, and saturated with HBr gas. The mixture was evaporated to dryness *in vacuo*, treated with a minimum volume of water and extracted repeatedly with ethyl acetate. The ethyl acetate layers were combined, dried over sodium sulfate, filtered, and evaporated to dryness *in vacuo* to give the title compound.

¹Bock, M.G., et al., J. Org. Chem., **52**, 3232 (1987).

EXAMPLE 12

(RS)-N-(2,3-Dihydro-1-(2-hydroxyethyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide
3-(RS)-Amino-1,3-dihydro-1-(2-hydroxyethyl)-5-phenyl-2H-1,4-benzodiazepin-2-one (69.0 mg, 0.234 mmole), indole-2-carbonyl chloride (43.1 mg, 0.240 mmole) and triethylamine (33.3 μ l, 0.240 mmole) were combined in CH₂Cl₂ (3 ml). The reaction was stirred for 10 minutes at room temperature then chromatographed on silica gel (14% acetone in CH₂Cl₂). The product fractions were combined and evaporated to dryness *in vacuo*. The residue was triturated with Et₂O to yield the title compound : (m.p. 160-171°C).

TLC : silica gel (15% acetone in CH₂Cl₂) R_f = 0.27
NMR : Consistent with structure
HPLC : 97.6% M.S. : Molecular ion at m/e = 438
Anal. Calc'd for C₂₆H₂₂N₄O₃·0.1C₄H₁₀O·0.25H₂O
C, 70.40 ; H, 5.26 ; N, 12.44
Found : C, 70.40 ; H, 5.16 ; N, 12.15

EXAMPLE 13

(RS)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-9H-pyrido(3,4-b)indol-3-yl-urea
A solution of (RS)-1,3-dihydro-1-methyl-3-(p-nitrophenyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one (100 mg, 0.232 mmole) and 3-amino- β -carboline¹ (45.8 mg, 0.250 mmole) in DMF (5 ml) was treated with triethylamine (48.4 μ l, 0.348 mmole) and warmed to 45°C for 16 hours. After removal of DMF *in vacuo*, the residue was dissolved in CH₂Cl₂ and chromatographed on silica gel (25% acetone in CH₂Cl₂). The product fractions were combined and stripped and the title compound crystallized from EtOAc : (m.p. 281-283°C).

TLC : silica gel (160/10/1 of CH₂Cl₂/MeOH/conc. NH₄OH) R_f = 0.24
NMR : Consistent with structure
HPLC : 99.3% pure
M.S. : M + H = 475 (FAB)
Anal. Calc'd for C₂₈H₂₂N₆O₂·0.20C₄H₈O₂

C, 70.28 ; H, 4.83 ; N, 17.08

Found : C, 70.10 ; H, 4.55 ; N, 17.24

¹Dodd, R. H., et al. J. Med. Chem. 28 824 (1985)5 EXAMPLE 14

(RS)-N-(6-Amino-3-pyridyl)-N'-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-urea
 2,5-Diaminopyridine dihydrochloride (45.5 mg, 0.250 mmole), (RS)-1,3-dihydro-1-methyl-3-(p-
 nitrophenyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one (100 mg, 0.232 mmole) and
 triethylamine (110 μ l, 0.79 mmole) were combined in DMF (8 ml) and stirred at room temperature for 16 hours.
 After removal of DMF *in vacuo*, the residue was treated with 1N NaOH (aqueous) and extracted with EtOAc
 (3x). The organic layers were combined, washed with brine (1x), dried over Na₂SO₄, filtered and evaporated
 to dryness *in vacuo*. The crude residue was chromatographed on silica gel eluted with 7% MeOH in CH₂Cl₂.
 The product fractions were combined and evaporated to dryness *in vacuo*. The residue was crystallized from
 EtOAc diluted with Et₂O to give the title compound : (m.p. 165-175°C).
 TLC : silica GF (90/10/1/1 of CH₂Cl₂/MeOH/H₂O/HOAc) R_f = 0.22
 NMR : consistent with structure
 HPLC : 96.3%
 M.S. : M + H = 401 (FAB)
 Anal. Calc'd for C₂₂H₂₀N₆O₂·0.35H₂O

C, 64.96 ; H, 5.13 ; N, 20.66

Found : C, 65.05 ; H, 5.20 ; N, 20.66.

25 EXAMPLE 15

1,3-Dihydro-3-(5-hydroxyindole-2-carboxylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one
 3(S)-(-)-3-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (0.14 g, 0.53 mmol) and 5-
 hydroxyindole-2-carboxylic acid (0.11 g, 0.63 mmol) were combined in a mixture of CH₂Cl₂ (5 ml) and DMF (1
 ml). EDC (0.1 g, 0.56 mmol) was added followed by Et₃N sufficient to render the mixture basic (pH 8) to mois-
 tened pH detector sticks (E. Merck). The mixture was stirred at ambient temperature for 6 hours, then evapo-
 rated to dryness *in vacuo*. The residue was diluted with aqueous citric acid and extracted with EtOAc. The
 EtOAc layer was washed twice with saturated sodium bicarbonate which had been diluted 1 : 1 with water, then
 dried over sodium sulfate, filtered, and evaporated to dryness *in vacuo*. The residue was dried *in vacuo* at 90°C
 overnight to give the title compound : (mp 120-130°C (↑)).
 TLC : Silica gel (10% CH₃OH in CH₂Cl₂) R_f = 0.73
 NMR : Consistent with structure, H₂O observed.
 HPLC : Greater than 94.5% pure
 M.S. Molecular ion at m/e = 424
 Anal. Calc'd for C₂₅H₂₀N₄O₃·0.55H₂O :

C, 69.12 ; H, 4.90 ; N, 12.90 ;

Found : C, 69.34 ; H, 5.01 ; N, 12.52.

45 EXAMPLE 16

1,3-Dihydro-3-(5-carboxymethyloxyindole-2-carboxylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-
 one
 1,3-Dihydro-3-(5-hydroxyindole-2-carboxylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (0.1 g,
 0.236 mmol) and iodoacetic acid (0.044 g, 0.236 mmol) were combined in dry DMF (2 ml) and treated with
 sodium hydride (18.8 mg of a 60% suspension in mineral oil ; 0.472 mmol). The mixture was stirred at ambient
 temperature for 1 hour, then evaporated to dryness *in vacuo*. To the residue were added water, dilute sodium
 bisulfite solution, then saturated sodium bicarbonate. The aqueous phase was washed with EtOAc, made acidic
 with 6N HCl, and extracted with EtOAc. The acid layer extract was dried over sodium sulfate, filtered, and evapo-
 rated to dryness *in vacuo*. The residue was chromatographed on silica gel eluted with 180 : 10 : 1 : 1 of CH₂Cl₂ :
 MeOH : HOAc : H₂O. The product fractions were evaporated to dryness *in vacuo* and the residue triturated with
 ether to give the title compound which was dried *in vacuo* at 90°C overnight : (mp 150-180°C (↑)).
 TLC : Silica gel (180 : 10 : 1 : 1 of CH₂Cl₂ : CH₃OH : HOAc : H₂O) R_f = 0.19

NMR : Consistent with structure, Et₂O and H₂O observed.

HPLC : Greater than 83.2% pure

M.S. M + H at m/e = 483 (FAB)

Anal. Calc'd for C₂₇H₂₂N₄O₅·0.05Et₂O·0.7H₂O :

C, 65.49 ; H, 4.83 ; N, 11.23 ;

Found : C, 65.53 ; H, 4.49 ; N, 11.10.

EXAMPLE 17

N-(2,3-Dihydro-1-(2-hydroxyethyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)-urea
3-(RS)-Amino-1,3-dihydro-1-(2-hydroxyethyl)-5-phenyl-2H-1,4-benzodiazepin-2-one (0.45 g, 1.5 mmol) was dissolved in THF (10 ml) and treated with 3-methylphenylisocyanate (0.207 g, 1.55 mmol), and the mixture stirred at ambient temperature for 1 hour, then evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 20% acetone in CH₂Cl₂. The product fractions were evaporated to dryness in vacuo and the residue triturated with ether to give the title compound which was dried in vacuo at 65°C for 2 hours : (mp 138-154°C).

TLC : Silica gel (90 : 4 : 0.4 : 0.4 of CH₂Cl₂ : CH₃OH : HOAc : H₂O) R_f = 0.24

NMR : Consistent with structure.

HPLC : Greater than 99.7% pure

M.S. M + H at m/e = 429 (FAB)

Anal. Calc'd for C₂₅H₂₄N₄O₃·0.07 Et₂O·0.4 H₂O :

C, 68.87 ; H, 5.83 ; N, 12.71 ;

Found : C, 68.83 ; H, 5.63 ; N, 12.58.

EXAMPLE 18

N-(2,3-Dihydro-1-(2-dimethylaminoethyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methoxyphenyl)-urea

Sodium hydride (26.4 mg of a 50% dispersion in mineral oil ; 0.55 mmol) was stirred under nitrogen in dry DMF (5 ml) in an ice bath. (RS)-1,3-Dihydro-3-(benzyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one (0.21 g, 0.54 mmol) in DMF (4 ml) was added, and the mixture stirred 1 hr in the cold. (2-Chloroethyl)-dimethylamine (59.2 mg, 0.55 mmol), prepared by distillation of a mixture of the hydrochloride and powdered sodium hydroxide in vacuo, was added and the mixture stirred 1 hr in the cold, and overnight at ambient temperature. The DMF was removed in vacuo and the residue was treated with water and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 90 : 10 : 1 : 1 of CH₂Cl₂ : MeOH : H₂O : HOAc and the product fractions were evaporated to dryness in vacuo to provide (RS)-1-(2-chloroethyl)-1,3-dihydro-3-(benzyloxycarbonyl)-amino-5-phenyl-2H-1,4-benzodiazepin-2-one. This compound (120 mg, 0.268 mmol) was added to a suspension of 10% palladium/Carbon (70 mg) in 4.5% methanolic formic acid (5 ml) stirred at ambient temperature under nitrogen. After 25 min, the mixture was filtered and the filtrate evaporated to dryness in vacuo. The residue was treated with saturated sodium carbonate solution and extracted with ethyl acetate. The combined ethyl acetate layers were washed with water, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was dissolved in THF, cooled in an ice bath, and treated with 3-methoxyphenylisocyanate (35.1 µl). The mixture was stirred in the cold for 30 min, warmed to ambient temperature, and filtered. The filtrate was evaporated to dryness in vacuo, and the residue was treated with ether (30 ml) and re-evaporated three times. The residue was triturated with ether and filtered, and the resulting solid dried at 65°C overnight to provide the title compound : (mp 213-215°C).

TLC : Silica gel (80 : 10 : 1 of CH₂Cl₂ : CH₃OH : NH₃) R_f = 0.41

NMR : Consistent with structure.

HPLC : Greater than 99.3% pure

M.S. M + H at m/e = 472 (FAB)

Anal. calc'd for C₂₇H₂₉N₅O₃ :

C, 68.77 ; H, 6.20 ; N, 14.85 ;

Found : C, 68.43 ; H, 6.30 ; N, 14.75.

EXAMPLE 19

(R)-3-((((2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)amino)carbonyl)amino)benzoic acid ethyl ester

5 (R)-1,3-Dihydro-1-methyl-3-(p-nitrophenyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one (150 mg, 0.35 mmol), 3-aminobenzoic acid ethyl ester (61 mg, 0.37 mmol), and triethylamine (52.5 mg, 0.52 mmol) were combined in DMF (2 ml) and heated at 45° overnight. The DMF was removed in vacuo and the residue crystallized from ethyl acetate to provide the title compound : (mp 140-142°C).

TLC : Silica gel (1 : 1 ethyl acetate : hexane) R_f = 0.27

10 NMR : Consistent with structure.

HPLC : Greater than 96.6% pure

M.S. Molecular ion at m/e = 456

Anal. calc'd for $C_{26}H_{24}N_4O_4 \cdot 0.5H_2O$:

15 C, 67.09 ; H, 5.41 ; N, 12.04 ;

Found : C, 67.09 ; H, 5.25 ; N, 11.87.

EXAMPLE 20

20 (R)-3-((((2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)amino)carbonyl)amino) acetic acid

(R)-1,3-Dihydro-1-methyl-3-(p-nitrophenyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one (1.92 g, 4.47 mmol) was dissolved in THF (25 ml) and treated with a solution of (3-aminophenyl)acetic acid methyl ester (670 mg, 4.06 mmol) in THF (5 ml) followed by triethylamine (615 mg, 6.09 mmol). The mixture was stirred at ambient temperature for 4 days. The solvent was removed in vacuo and the residue was treated with water (20 ml) and extracted with ethyl acetate. The combined ethyl acetate layers were washed with 1 M NaOH, then with 10% citric acid, dried over sodium sulfate, filtered and evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 1 : 1 hexane : ethyl acetate. The product fractions were combined and evaporated to dryness in vacuo and the residue crystallized from ethyl acetate to give (R)-3-
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(((2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)amino)carbonyl)amino)phenyl acetic acid methyl ester. This ester (885 mg, 1.94 mmol) was dissolved in THF (5 ml) and treated with a solution of lithium hydroxide (815 mg, 19.4 mmol) in water (10 ml). The mixture was stirred at ambient temperature for 3 hours, diluted with water (100 ml), acidified with 1N HCl, and extracted with ethyl acetate. The ethyl acetate layers were washed with brine, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with chloroform followed by 9 : 1 chloroform : methanol. The product fractions were combined and evaporated to dryness in vacuo. The residue was crystallized from ethyl acetate to provide the title compound : (mp 167-170°C).

TLC : Silica gel (1 : 1 ethyl acetate : hexane) single component.

NMR : Consistent with structure.

40 HPLC : Greater than 97% pure.

M.S. $M + H$ at m/e = 443 (FAB).

Anal. Calc'd for $C_{25}H_{22}N_4O_4 \cdot 0.55EtOAc$:

C, 66.54 ; H, 5.42 ; N, 11.41 ;

45 Found : C, 66.15 ; H, 5.04 ; N, 11.63.

EXAMPLE 21

50 (R)-N-(2,3-Dihydro-1H-inden-5-yl)N'-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)urea

(R)-1,3-Dihydro-1-methyl-3-(p-nitrophenyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one (200 mg, 0.46 mmole) was dissolved in 2 ml of freshly degassed, dry N,N-dimethylformamide (DMF) and treated with 1 ml of DMF containing 74 mg (0.50 mmole) of 5-aminoindane and 97.4 μ l of triethylamine. The resulting solution was stirred under nitrogen for four hours. The reaction mixture was poured into 75 ml of water and
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extracted with ethyl acetate (3 x 40 mL). The combined organic extracts were washed with 1 N sodium hydroxide solution (4 x 100 mL), 10% citric acid solution (2 x 100 mL), and brine. The organic extracts were then dried and the residue was plug-filtered through a six inch silica gel column. The eluate was concentrated and the residue was crystallized from a methylene chloride-ether mixture to give the title compound : mp 156-158°C

NMR : Structure is consistent with the spectrum.

FAB MS : 425 ($M^+ + H$).

Anal. Calc'd for $C_{26}H_{24}N_4O_2$:

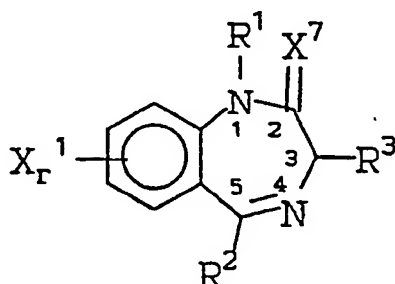
Calc'd : C, 73.56 ; H, 5.69 ; N, 13.20.

5 Found : C, 73.26 ; H, 5.81 ; N, 13.04.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations or modifications, as come within the scope of the following claims and its equivalents.

Claims

1. A compound of Formula :

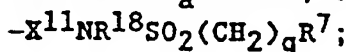
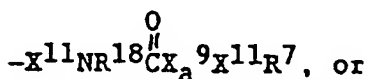
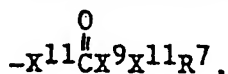
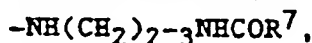
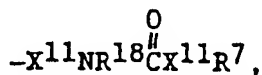


wherein :

R¹ is H, C₁-C₈ linear or branched alkyl, loweralkenyl, lower alkynyl, X¹²COOH, -X¹²COOR⁶, -X¹¹-cycloloweralkyl, -X¹²NR⁴R⁵, -X¹²CONR⁴R⁵, -X¹²CN, or -X¹¹CX₃¹⁰ ;

R² is H, loweralkyl, substituted or unsubstituted phenyl (wherein the substituents may be 1 or 2 of halo, loweralkyl, loweralkoxy, loweralkylthio, carboxyl, carboxyloweralkyl, nitro, -CF₃, or hydroxy), 2-, 3-, or 4-pyridyl ;

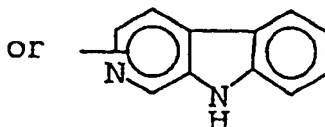
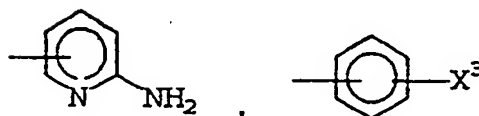
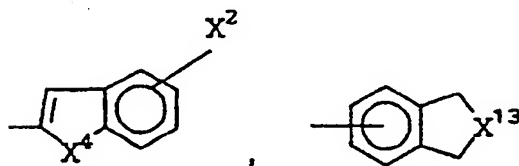
R³ is



R⁴ and R⁵ are independently H or R⁶ or in combination with the N of the NR⁴R⁵ group form an unsubstituted or mono or disubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring, or benzofused, 4-7 membered heterocyclic ring wherein said heterocyclic ring or said benzofused heterocyclic ring may contain a second heteroatom selected from O and NCH₃ and the substituent(s) is/are independently selected from C₁-C₄alkyl ;

R⁶ is loweralkyl, cycloloweralkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted phenylloweralkyl wherein the phenyl or phenylloweralkyl substituents may be 1 or 2 of halo, loweralkyl, loweralkoxy, nitro, or CF₃ ;

R⁷ is

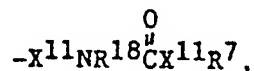


R⁸ is H, loweralkyl, cycloloweralkyl, -X¹³CONH₂, -X¹³COOR⁶, -X¹³COOH, -X¹³-cycloloweralkyl, or -X¹³NR⁴R⁵;
 R¹⁵ is H, or loweralkyl;
 R¹⁶ is H or loweralkyl ;
 n is 1-6,
 q is 0-4 ;
 r is 1 or 2 ;
 X¹ is H, -NO₂, CF₃, CN, OH, loweralkyl, halo, loweralkylthio, loweralkoxy, -X¹¹COOR⁶, X¹¹COOH, or -X¹¹NR⁴R⁵;
 X² is H or X³, with the proviso that when X² is H, then X⁴ is NX⁵COOH or NX⁵COOR⁶ wherein X⁵ is a linear alkyl chain of 2 to 6 carbon atoms, any carbon atom of which may be additionally substituted with a linear or branched alkyl group of 1 to 3 carbon atoms ;
 X³ is O(CH₂)_nCOOR⁶, O(CH₂)_nCOOH, (CH₂)_nCOOR⁶, (CH₂)_nCOOH, COOR⁶, or X¹²OR⁶ ;
 X⁴ is S, O, CH₂, or NR⁸ ;
 X⁷ is O, S, HH, or NR¹⁵ with the proviso that X⁷ can be NR¹⁵ only when R¹ is not H ;
 X⁸ is H, loweralkyl ;
 X⁹ and X⁹ are independently NR¹⁶ or O ;
 X¹⁰ is F, Cl, or Br ;
 X¹¹ is absent or C₁₋₄ linear or branched alkyl ;
 X¹² is C₁₋₄ linear or branched alkylidene,
 X¹³ is C₁₋₄ linear or branched alkyl ;

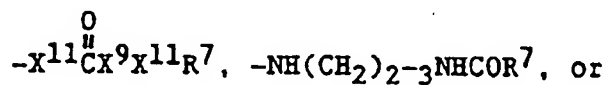
or pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein :

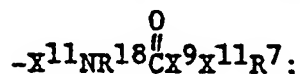
- 5 R^1 is H, C_1 - C_8 linear or branched alkyl, $-X^{12}COOR^6$, $-X^{11}$ -cycloalkyl, $X^{12}NR^4R^5$, $-X^{12}CONR^4R^5$, or $X^{12}COOH$;
- R^2 is substituted or unsubstituted phenyl (wherein the substituents may be 1 or 2 of halo, loweralkyl, loweralkoxy, loweralkylthio, carboxyl, carboxyloweralkyl, nitro, $-CF_3$ or hydroxy), 2-, 3-, or 4- pyridyl ;
- 10 R^3 is



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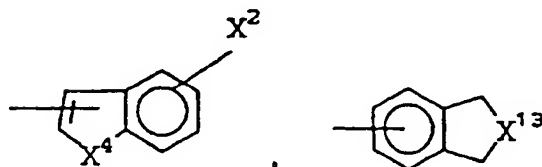


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- R^4 and R^5 are independently H or R^6 or in combination with the N or the NR^4R^5 group form an unsubstituted or mono or disubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring, or benzofused 4-7 membered heterocyclic ring wherein said heterocyclic ring or said benzofused heterocyclic ring may contain a second heteroatom selected from O and NCH_3 and the substituent(s) is/are independently selected from C_1 - C_4 alkyl ;
- 30 R^6 is C_{1-4} straight or branched-chain alkyl or C_3 - C_6 cycloalkyl ;
- R^7 is

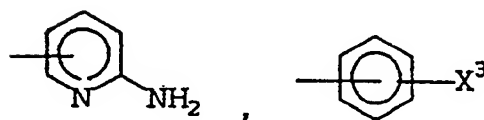
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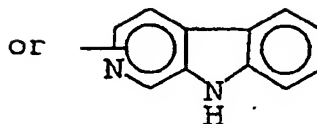


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R^8 is H, loweralkyl, cycloloweralkyl, $X^{13}COOR^6$, $X^{13}COOH$, or $X^{13}NR^4R^5$;

R^{18} is H or loweralkyl;

n is 1-3;

q is 0-3;

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r is 1 or 2;

X^1 is H, $-NO_2$, CF_3 , CN, loweralkyl, halo, loweralkylthio, $-X^{11}COOR^6$, $X^{11}COOH$, or $X^{11}NR^4R^5$;

X^2 is H or X^3

with the proviso that when X^2 is H, then X^4 is NX^5COOH or NX^5COOR^6 wherein X^5 is a linear alkyl chain of 2 to 4 carbon atoms, any carbon atom of which may be additionally substituted with a linear or branched alkyl group of 1 to 3 carbon atoms;

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X^3 is $O(CH_2)_nCOOR^6$, $O(CH_2)_nCOOH$, $(CH_2)_nCOOR^6$, $(CH_2)_nCOOH$, or $COOR^6$;

X^4 is S, O, or NR^8 ;

X^7 is O;

X^9 and X_{a^9} are independently NR^{18} , or O;

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X^{11} is absent or C_{1-4} linear alkyl;

X^{12} is C_{1-4} linear or branched alkylidene;

X^{13} is C_{1-4} linear or branched alkyl;
or pharmaceutically acceptable salt thereof.

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3. The use of a compound as claimed in claim 1 or claim 2 for the manufacture of a medicament for antagonizing the binding of cholecystokinin to cholecystokinin receptors or antagonizing the binding of gastrin to gastrin receptors.

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4. A pharmaceutical composition useful in the treatment of disorders of gastric secretion, appetite regulation, gastrointestinal motility, pancreatic secretion, and dopaminergic function, comprising an effective amount of a compound of claim 1 or claim 2 in association with a pharmaceutically acceptable carrier.

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Office

PARTIAL EUROPEAN SEARCH REPORT
which under Rule 45 of the European Patent Convention
shall be considered, for the purposes of subsequent
proceedings, as the European search report

Application number

EP 90 31 3854

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 32, no. 1, January 1989, pages 13-16, American Chemical Society, Washington, DC, US; M.G. BOCK et al.: "Benzodiazepine gastrin and brain cholecystokinin receptor ligands: L-365,260" * Whole article *	1,3,4	C 07 D 243/24 C 07 K 5/06 C 07 D 401/12 C 07 D 471/04 A 61 K 31/55 A 61 K 37/02/ (C 07 D 471/04 C 07 D 221:00 C 07 D 209:00)
A	EP-A-0 304 223 (MERCK) * Pages 3-6 *	1,3,4	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 D 243/00 C 07 D 471/00 C 07 D 401/00 C 07 K 5/00
INCOMPLETE SEARCH			
<p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.</p> <p>Claims searched completely: 1-4</p> <p>Claims searched incompletely:</p> <p>Claims not searched:</p> <p>Reason for the limitation of the search:</p> <p>As the drafting of the claims is not concise (Art. 84 EPC) and encompasses an enormous number of compounds not supported by the description, the search has been carried out, on economic grounds, on the basis of the claimed examples (Guidelines for Examination in the EPO, Part B, Chapter III, 3.7).</p>			
Place of search THE HAGUE		Date of completion of the search 14-03-1991	Examiner ENGLISH
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

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